

Subcutaneous versus Sublingual Immunotherapy for Allergic Rhinitis therapy: Which Is Superior

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Abstract: Background: A randomized single-blinded study including 50 patients with allergic rhinitis. Objective: To evaluate and compare the efficacy of subcutaneous versus sublingual immunotherapy in treatment of allergic rhinitis. Materials and methods: Patients divided into Group A: twenty patients received subcutaneous immunotherapy and group B: twenty patients received sublingual immunotherapy for twelve months. We assessed skin prick test, symptom score and medication use, quality of life and nasal smear eosinophilic count before and after treatment. Results: In group A, clinical improvement was achieved in 100% of monosensitized and 62.5% of polysensitized patients, while in group B 100% of monosensitized and 60% of polysensitized patients exhibited clinical improvement. Conclusion: The subcutaneous and sublingual routes of immunotherapy have similar efficacy.

Keywords: Allergen Specific Immunotherapy, SCIT, SLIT, Allergic Rhinitis, Skin Prick Test, Nasal Smear Eosinophilia, Clinical Improvement

1. Introduction

Allergic rhinitis (AR) is an IgE-mediated inflammation of the upper airway that involves inflammation of the mucous membranes of the nose, eyes, Eustachian tubes, middle ear, sinuses, and pharynx [1]. Immunotherapy, both subcutaneous (SCIT) and sublingual (SLIT), is an effective treatment for adults and children with severe AR not responding to allergen avoidance measures and conventional pharmacotherapy [2]. Although AR is the disease in which SCIT efficacy is most documented and proved [3], constraints of the injective route and possibility of severe systemic reactions led to continuous research for alternative routes (nasal, oral, bronchial and sublingual), with the sublingual route generating most interest [4]. The clinical effect of both modalities lasts at least 3 years after stopping treatment [5].

The main aim of our study was to evaluate and compare the long term clinical efficacy of SCIT versus SLIT in treatment of patients with AR.

2. Materials and Methods

Our study was a randomized single-blinded study including 50 patients with moderate to severe AR recruited from Allergy outpatient clinic at Ain Shams and Zagazig University Hospitals from May 2013 till September 2014. The study was approved by the local ethics committee and all patients gave informed oral consent. Diagnosis of AR conformed to ARIA Guidelines 2010 revision [6].

Table 1. Allergen extracts included in skin prick test.

Mixed molds	Mixed pollen	House dust
Mite	Wool	Tobacco
Candida	Latex	Goat hair
Hay dust	Feather	Pigeon
Cat hair	Cotton dust	Dog hair
Cockroaches		

Skin prick test (SPT) was done to identify allergen/allergens for which they will receive immunotherapy. We included patients with a positive SPT to 1 up to a maximum of 3 of the commonest locally encountered aeroallergens. The test panel was prepared at the Allergy and Clinical Immunology Unit laboratory at Ain Shams University hospitals (table 1).

Exclusion criteria included patients with positive SPT to more than 3 aeroallergens, inflammatory or septic conditions, patient with end organ failure, patients who received steroids, cytotoxic drugs or immunosuppressives one month prior to sample collection.

Of the 50 patients, 5 withdrew from each group due to poor adherence to treatment, relocation and pregnancy. Remaining patients were divided into two groups.

Group A: 20 patients received SCIT and group B: 20 patients received SLIT.

Both groups received immunotherapy for 12 months. The items assessed before and after the duration of treatment included SPT, patient symptom score, medication use, quality of life and nasal smear eosinophilic count.

2.1. Skin Prick Test (SPT)

SPT was performed on healthy skin on the volar surface of the forearm at 3-cm intervals. A lancet (Dome-Hollister-Stier) was used to prick the skin at a 90° angle through a drop of test solution on the skin [7]. A drop of histamine phosphate and a drop of saline 0.9% were used as a positive control and negative control respectively. The immediate response was evaluated after 20 minutes. A wheal diameter ≥ 3 mm more than the negative control was considered to be positive [8].

2.2. Quality of Life

The Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) was used, comprised of 14 questions (items) in five domains (activity limitations, sleep impairment, practical problems, nasal symptoms, eye symptoms and emotional problems) [9].

2.3. Medication Use

Medication usage was scored on a 4-point scale (table 2).

Table 2. Medication score.

0 = no rhinitis medication
1 = oral antihistamines
2 = topical corticosteroids
3 = systemic corticosteroids

Patients were considered improved if the total score decreased by one or more points [10].

2.4. Nasal Smear Eosinophilia

Anterior rhinoscopy was performed after application of a local vasoconstrictor (xylometazoline 0.1%). With a cotton swab, a smear was taken from the posterior part of the

inferior or middle turbinate. The secretions were spread out to a thin layer on a glass slide and air-dried. Later, the smear was stained by the May-Griinwald- Giemsa method for microscopic evaluation [11].

2.5. Allergen-specific Immunotherapy (SIT)

A) Subcutaneous immunotherapy (SCIT):

Extracts were prepared as an aqueous solution using the weight/volume (wt/vol) method. A potency of 1:100 indicates that 1 g of dry allergen was added to 100 cc of a buffer (phenol saline) for extraction. The allergen was eluted for a time, and then the solid material was filtered out, leaving an aqueous solution [12].

Injections were administered with a 1-ml syringe. The injections were administered subcutaneously in the posterior portion of the middle third of the upper arm [13].

Dose: Allergen extract was diluted to have final dilutions 1:100, 1:1000 and 1:10000. The starting point was 0.2 ml of a 1:10000 dilution. The injections were twice weekly and the dose was increased weekly: 0.2, 0.4, 0.6, 0.8 and 1ml. The procedure was repeated with the next higher concentrations until the maintenance dose was reached.

Premedication: Patients were prescribed oral antihistamines 2 hours before each injection to reduce the frequency of any systemic reactions [13].

B) Sublingual immunotherapy (SLIT):

Extracts were prepared as glycerinated solution, using the wt/vol method [14]. Extract was administered on an empty stomach as sublingual drops kept under the tongue for 2 minutes then swallowed.

Dose: Treatment was divided into build-up and maintenance phases. Allergen extract was diluted to have final dilutions 1:50, 1:500 and 1:5000. The starting dose was 3 drops daily of 1:5000 dilution for one week, then 5 drops daily for the second week, then 7 drops daily for another third week. The procedure was repeated with the next higher concentrations until the maintenance dose was reached, which was 5 drops of 1:50 dilution. The maintenance dose was given every other day for 3 weeks then every 3 days for 6 weeks then every week for a total of 12 months.

Statistical Analysis:

Analysis of data was performed on a personal computer using Graph Pad Prism version 5, as follows:

1. Description of quantitative variables using mean, standard deviation (SD) and range.
2. Description of qualitative variables using number and percentage.
3. Unpaired t-test was used to determined significant differences between two different groups.
4. Paired t-test was used to determined significant differences within the same group.
5. The level of significance was ($p < 0.05$).

3. Results

Baseline demographic and clinical characteristics are displayed in table 3. Regarding SPT in group A, 4 patients

(20%) were monosensitized, 2 patients for house dust mites, 1 for pollens, 1 for pigeon feather and 16 patients were polysensitized. For group B, 5 patients (25%) were monosensitized, 3 patients for pollens, 1 for hay dust, 1 for house dust mites and 15 patients were polysensitized.

Regarding SPT, patients were considered improved if the test became negative or number of positive allergens diminished after 12 months of immunotherapy, while persistence of the same allergens or appearance of new allergens denoted that the patient didn't improve (fig 1). Table 4 shows number of patients who showed clinical improvement in both groups. Although there was statistically significant improvement in both the SCIT group and SLIT group after administering immunotherapy, we could not detect statistically significant difference between both groups after treatment indicating equal efficacy of both SCIT and SLIT in causing clinical improvement of allergic rhinitis patients after 12 months of SIT. Single-allergen preparations were clearly more effective than multi-allergen preparations in control of symptoms and improvement of the patient in both studied groups. As illustrated in table 4 Fig. (2), comparing the pre and post treatment medication use mean values were 1.950 ± 0.223 and 1.250 ± 0.638 for group A (SCIT) and 1.950 ± 0.223 and 1.33 ± 0.656 for group B (SLIT) which indicated statistically significant difference in each group between the pre and post treatment ($p < 0.05$). As illustrated in Fig. (3), when comparing the pre and post treatment nasal smear eosinophilia mean values were 7.65 ± 3.06 and 5.20 ± 3.31 for SCIT group and 8.8 ± 2.33 and 4.9 ± 3.024 for SLIT group indicating statistically significant difference in both groups post treatment ($p < 0.05$).

Regarding side effects noted, in SCIT group 13 patients experienced local redness and edema at the injection site, 1 patient had overall itching, 2 patients experienced acute asthmatic attacks. In SLIT group, 1 patient complained of diarrhea and abdominal pain, 1 patient had oral itching, and 1 patient had an asthmatic attack.

Table 3. Baseline demographic and clinical characteristics of the 2 groups.

Variable	Group A (n=20)	Group B (n=20)
Age, year	36.8 (9.277)	29.3 (11.75)
Male/Female ratio	8/12	15/5
Medication score	1.950 (0.233)	1.950 (0.233)
Baseline mini RQLQ	43.30 (8.64)	35.55 (9.67)
Nasal smear eosinophilia (%)	7.65 (3.06)	8.8 (2.33)

Data presented as mean (SD) or number (%)

Table 4. Number (%) of patients who showed clinical improvement (mini RQLQ) in both groups.

Item	Monosensitized patients	Polysensitized patients
No of improved patients Group A	(4)100%	(10)62.5%
No of improved patients Group B	(5)100%	(9)60%

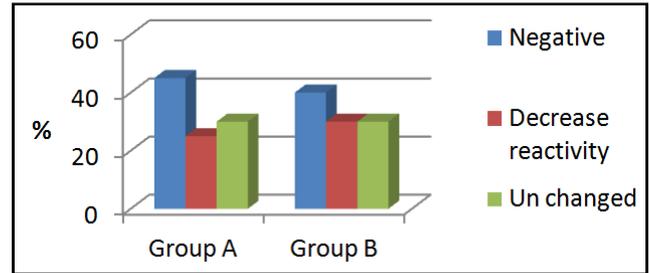


Fig. (1). The Skin prick test in both group A (SCIT) and group B (SLIT) after 12 months of treatment.

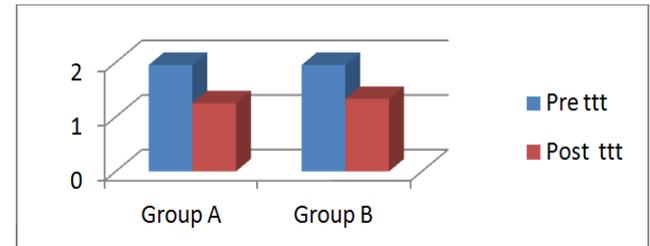


Fig. (2). Medication score of each SCIT and SLIT group before and after treatment.

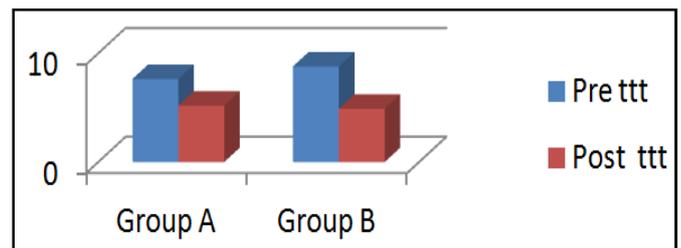


Fig. (3). Nasal smears eosinophilia of each SCIT and SLIT group before and after treatment.

4. Discussion

AR represents a major cause of morbidity that includes interference with usual daily activities and impairment of sleep quality [15]. Immunotherapy can be administered by different routes; the classical SCIT usually known as "allergy shots." and SLIT where the allergens are administered as drops to the sublingual area [16]. Side effects reported after immunotherapy in our study were more pronounced in the SCIT rather than SLIT group.

In both groups we found clinical improvement after 12 months of treatment, with marked reduction in medication use; 4 patients stopped their medications completely.

A systematic review done concluded there was significant reduction of symptom and medication scores following SLIT, however all studies included in the meta analysis administered SLIT in comparison to placebo rather than SCIT [17].

In 15 studies published between 2000 and 2006, reduction of symptoms and/or need for medications were confirmed with grass, birch, parietaria, ragweed pollens and house dust mites in SCIT treated patients. However, all of the studies included in the meta-analysis compared the efficacy of SCIT to placebo [18].

Another Cochrane meta-analysis of 42 double-blind, placebo-controlled studies showed significant reduction in rhinitis symptoms and medication requirements after SLIT [19].

Kim and Colleagues compared multiallergen SCIT in polysensitized patients with single-allergen SCIT in monosensitized patients. The study investigated 130 children treated for 18 months. In both groups the mean postallergen immunotherapy symptom scores were significantly ($P < 0.05$) lower than preallergen immunotherapy. However, the reduction was significantly less intense in the polysensitized group [20].

Reduced skin test reactivity after immunotherapy was observed in both groups; this may be explained by the fact that SIT leads to an increase of allergen-specific IgG, especially IgG4, which leads to inhibition of IgE-facilitated antigen presentation and inhibition of IgE-mediated release of mediators from mast cells and basophils [21].

Similarly, Eifan and Colleagues also found that SPT response significantly decreased in both SLIT and SCIT groups compared to baseline [22]. Nasal smear eosinophil counts in both groups of this study exhibited a significant reduction after therapy, although not reaching statistical significance.

SIT was found to decrease the recruitment of mast cells, basophils, and eosinophils to the skin, nose, eye, and bronchial mucosa after exposure to allergens [23].

To our knowledge, only a few studies have directly compared SCIT and SLIT [3]. Ours is one of the very few studies to directly compare SCIT and SLIT regarding both clinical and immunologic parameters. In 2004, the first study comparing efficacy of SLIT versus SCIT in AR is yet considered as the only adequate methodological trial (placebo controlled, double blind, double dummy) [24], concluding that both SCIT and SLIT are clinically effective compared with placebo in treatment of birch pollen rhinoconjunctivitis.

We report comparable efficacy of SCIT and SLIT for AR treatment, with improvement in symptom control and reduced medication use. SLIT represents a more suitable alternative to SCIT suitable for home use and with a better safety profile and less adverse effects. Single allergen immunotherapy was more effective than multi-allergen immunotherapy. Since the indications of both types of immunotherapy are similar, the patient's choice is crucial in deciding whether to use the subcutaneous or sublingual route. There remains a need for larger double-blinded controlled long-term studies on immunotherapy with perennial allergens.

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